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Med Choice CNS

℞

Clozapine

Clozadin ®

25 mg and 100 mg Tablet
ANTIPSYCHOTIC

FORMULATION:
Each tablet contains:
Clozapine ..... 25 mg
Clozapine ..... 100 mg

PRODUCT DESCRIPTION:
Clozapine (Clozadin) 25 mg- Yellow, round, normal convex, tablets, scored on one side tablets.
Clozapine (Clozadin) 100 mg- Yellow, round, normal convex, tablets, crossed tablets.

PHARMACOLOGICAL PROPERTIES:
Pharmacodynamic properties
Pharmacotherapeutic group: Psycholeptics; antipsychotics, ATC Code: N05AH02
Mechanism of action
Clozapine has been shown to be an antipsychotic agent that is different from classic antipsychotics.
In pharmacological experiments, the compound does not induce catalepsy or inhibit apomorphine or amphetamine-induced stereotyped behavior. It has only weak dopamine-receptor-blocking activity at D1, D2, D3, and D5 receptors, but shows high potency for the D4 receptor.
Pharmacodynamic effects
Clozapine has potent anti-alpha-adrenergic, anticholinergic, antihistaminic, and arousal-reaction inhibiting effects. It has also been shown to possess antiserotoninergic properties.
Clinical efficacy and safety
Clinically, clozapine produces rapid and marked sedation and exerts antipsychotic effects in schizophrenic patients resistant to other drug treatments. In such cases, clozapine has proven effective in relieving both positive and negative schizophrenic symptoms mainly in short-term trials. In an open clinical trial performed on 319 treatment-resistant patients treated for 12 months, a clinically relevant improvement was observed in 37% of patients within the first week of treatment and in an additional 44% by the end of 12 months. The improvement was defined as about a 20% reduction from the baseline in Brief Psychiatric Rating Scale Score. In addition, improvement in some aspects of cognitive dysfunction has been described.
Compared to classic antipsychotics, clozapine produces fewer major extrapyramidal reactions such as acute dystonia, parkinsonian-like side effects, and akathisia. In contrast to classic antipsychotics, clozapine produces little or no prolactin elevation, thus avoiding adverse effects such as gynecomastia, amenorrhea, galactorrhea, and impotence.
A potentially serious adverse reaction caused by clozapine therapy is granulocytopenia and agranulocytosis occurring at an estimated incidence of 3% and 0.7%, respectively. In view of this risk, the use of clozapine should be limited to patients who are treatment-resistant or patients with psychosis in Parkinson's disease when other treatment strategies have failed and in whom regular hematological examinations can be performed.
Pharmacokinetic properties
Absorption
The absorption of orally administered clozapine is 90 to 95%; neither the rate nor the extent of absorption is influenced by food.
Clozapine is subject to moderate first-pass metabolism, resulting in an absolute bioavailability of 50 to 60%.
Distribution
In steady-state conditions, when given twice daily, peak blood levels occur on an average of 2.1 hours (range: 0.4 to 4.2 hours), and the volume of distribution is 1.6 L/kg. Clozapine is approximately 95% bound to plasma proteins.
Biotransformation/metabolism
Clozapine is almost completely metabolized before excretion by CYP1A2 and CYP3A4, and to some extent by CYP2C19 and CYP2D6. Of the main metabolites only the desmethyl metabolite was found to be active. Its pharmacological actions resemble those of clozapine but are considerably weaker and of short duration.
Elimination
Its elimination is biphasic, with a mean terminal half-life of 12 hours (range: 6 to 26 hours). After single doses of 75 mg the mean terminal half-life was 7.9 hours; it increased to 14.2 hours when steady-state conditions were reached by administering daily doses of 75 mg for at least 7 days.
Only trace amounts of unchanged drugs are detected in the urine and feces, approximately 50% of the administered dose being excreted as metabolites in the urine and 30% in the feces.
Linearity/non-linearity
Dosage increases from 37.5 mg to 75 mg and 150 mg given twice daily were found to result during steady state in linearly dose-proportional increases in the area under the plasma concentration/time curve (AUC) and in the peak and minimum plasma concentrations.

THERAPEUTIC INDICATIONS:
Treatment-resistant schizophrenia
Clozapine is indicated in treatment-resistant schizophrenic patients and in schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics.
Treatment resistance is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for adequate duration.
Psychosis during the course of Parkinson's disease
Clozapine is also indicated in psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed.

DOSAGE AND ADMINISTRATION:
Posology
The dosage must be adjusted individually. For each patient, the lowest effective dose should be used. For doses not realizable/practicable with one strength, other strengths of this medicinal product are available. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.
Initiation of clozapine treatment must be restricted to those patients with a WBC count > 3500/mm^3 (3.5x109/L) and an ANC > 2000/mm^3 (2.0x109/L) within standardized normal limits.
Dose adjustment is indicated in patients who also receive medicinal products with pharmacodynamic and pharmacokinetic interactions with clozapine, such as benzodiazepines or selective serotonin reuptake inhibitors.
Switching from a previous antipsychotic therapy to clozapine
It is generally recommended that clozapine should not be used in combination with other antipsychotics. When clozapine therapy is to be initiated in a patient undergoing oral antipsychotic therapy, it is recommended that the other antipsychotic should first be discontinued by tapering the dosage downwards.
The following dosages are recommended:
Treatment-resistant schizophrenic patients
Starting therapy
12.5 mg once or twice on the first day, followed by 25 mg once or twice on the second day. If well tolerated, the daily dose may then be increased slowly in increments of 25 to 50 mg in order to achieve a dose level of up to 300 mg/day within 2 to 3 weeks. Thereafter, if required, the daily dose may be further increased in increments of 50 to 100 mg at half-weekly or, preferably, weekly intervals.
Therapeutic dose range:
In most patients, antipsychotic efficacy can be expected with 200 to 450 mg/day given in divided doses. The total daily dose may be divided unevenly, with the larger portion at bedtime.
Maximum dose
To obtain a full therapeutic benefit, a few patients may require larger doses, in which case judicious increments (not exceeding 100 mg) are permissible up to 900 mg/day. However, the possibility of increased adverse reactions (in particular seizures) occurring at doses over 450 mg/day must be borne in mind.
Maintenance dose
After achieving maximum therapeutic benefit, many patients can be maintained effectively on lower doses. Careful downward titration is therefore recommended. Treatment should be maintained for at least 6 months. If the daily dose does not exceed 200 mg, once daily administration in the evening may be appropriate.
Ending therapy
In the event of planned termination of clozapine therapy, a gradual reduction in dose over a 1- to 2-week period is recommended. If abrupt discontinuation is necessary, the patient should be carefully observed for the occurrence of withdrawal reactions.
Re-starting therapy
In patients in whom the interval since the last dose of clozapine exceeds 2 days, treatment should be re-initiated with 12.5 mg given once or twice on the first day. If this dose is well tolerated, it may be feasible to titrate the dose to the therapeutic level more quickly than is recommended for initial treatment. However, in any patient who has previously experienced respiratory or cardiac arrest with initial dosing, but was then able to be successfully titrated to a therapeutic dose, re-titration should be carried out with extreme caution.
Psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed
Starting therapy
The starting dose must not exceed 12.5 mg/day, taken in the evening. Subsequent dose increases must be by 12.5 mg increments, with a maximum of two increments a week up to a maximum of 50 mg, a dose that cannot be reached until the end of the second week. The total daily amount should preferably be given as a single dose in the evening.
Therapeutic dose range
The mean effective dose is usually between 25 and 37.5 mg/day. In the event that treatment for at least one week with a dose of 50 mg fails to provide a satisfactory therapeutic response, dosage may be cautiously increased by increments of 12.5 mg/week.
Maximum dose
The dose of 50 mg/day should only be exceeded in exceptional cases, and the maximum dose of 100 mg/day must never be exceeded.
Dose increases should be limited or deferred if orthostatic hypotension, excessive sedation, or confusion occurs. Blood pressure should be monitored during the first weeks of treatment.
Maintenance dose
When there has been complete remission of psychotic symptoms for at least 2 weeks, an increase in anti-parkinsonian medication is possible if indicated on the basis of motor status. If this approach results in the recurrence of psychotic symptoms, clozapine dosage may be increased by increments of 12.5 mg/week up to a maximum of 100 mg/day, taken in one or two divided doses.
Ending therapy
A gradual reduction in dose by steps of 12.5 mg over a period of at least one week (preferably two) is recommended.
Treatment must be discontinued immediately in the event of neutropenia or agranulocytosis. In this situation, careful psychiatric monitoring of the patient is essential since symptoms may recur quickly.
Special populations
Hepatic impairment
Patients with hepatic impairment should receive clozapine with caution along with regular monitoring of liver function tests.
Pediatric population
No pediatric studies have been performed. The safety and efficacy of clozapine in children and adolescents under the age of 16 years have not yet been established. It should not be used in this group until further data become available.
Patients 60 years of age and older
Initiation of treatment is recommended at a particularly low dose (12.5 mg given once on the first day), with subsequent dose increments restricted to 25 mg/day.
Method of administration: Oral administration
CONTRAINDICATIONS:
- Hypersensitivity to the active substance or to any of the excipients.
- Patients unable to undergo regular blood tests.
- History of toxic or idiosyncratic granulocytopenia/agranulocytosis (with the exception of granulocytopenia/agranulocytosis from previous chemotherapy).
- History of clozapine-induced agranulocytosis.
- Clozapine treatment must not be started concurrently with substances known to have a substantial potential for causing agranulocytosis; concomitant use of depot antipsychotics is to be discouraged.
- Impaired bone marrow function.
- Uncontrolled epilepsy.
- Alcoholic and other toxic psychoses, drug intoxication, comatose conditions.
- Circulatory collapse and/or CNS depression of any cause.
- Severe renal or cardiac disorders (e.g., myocarditis).
- Active liver disease associated with nausea, anorexia, or jaundice; progressive liver disease, hepatic failure.
- Paralytic ileus.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Agranulocytosis
Clozapine (Clozadin) can cause agranulocytosis. The incidence of agranulocytosis and the fatality rate in that developing agranulocytosis has decreased markedly since the institution of white blood cell (WBC) counts and absolute neutrophil count (ANC) monitoring. The following precautionary measures are therefore mandatory and should be carried out in accordance with official recommendations.
Because of the risks associated with clozapine, its use is limited to patients in whom therapy is indicated.
- who have initially normal leukocyte findings (WBC count ≥ 3500/mm^3 (3.5x109/L) and ANC ≥ 2000/mm^3 (2.0x109/L), and
- in whom regular WBC counts and ANC can be performed weekly for the first 18 weeks and at least 4-week intervals thereafter. Monitoring must continue throughout treatment and for 4 weeks after the complete discontinuation of clozapine.

Before initiating clozapine therapy, patients should have a blood test and a history and physical examination. Patients with a history of cardiac illness or abnormal cardiac findings on physical examination should be referred to a specialist for other examinations that might include an ECG, and the patient treated only if the expected benefits clearly outweigh the risks. The treating physician should consider performing a pre-treatment ECG.
White Blood Cell (WBC) counts and Absolute Neutrophil Count (ANC) monitoring WBC and differential blood counts must be performed within 10 days prior to initiating clozapine treatment to ensure that only patients with normal WBC counts and ANC (WBC count > 3500/mm^3 (3.5x109/L) and ANC > 2000/mm^3 (2.0x109/L) will receive clozapine. After the start of clozapine treatment, the WBC count and ANC must be performed and monitored weekly for the first 18 weeks, and at least at four-week intervals thereafter.
Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of clozapine or until hematological recovery has occurred. At each consultation, the patient must be reminded to contact the treating physician immediately if any kind of infection, fever, sore throat, or other flu-like symptoms develop. WBC and differential blood counts must be performed immediately if any symptoms or signs of an infection occur.
Low WBC count/ANC
If during clozapine therapy, either the WBC count falls to between 3500/mm^3 (3.5x109/L) and 3000/mm^3 (3.0x109/L) or the ANC falls to between 2000/mm^3 (2.0x109/L) and 1500/mm^3 (1.5x109/L), hematological evaluations must be performed at least twice weekly until the patient's WBC count and ANC stabilizes within the range 3000-3500/mm^3 (3.0-3.5x109/L) and 1500-2000/mm^3 (1.5-2.0x109/L), respectively, or higher.
Immediate discontinuation of clozapine treatment is mandatory if either the WBC count is less than 3000/mm^3 (3.0x109/L) or the ANC is less than 1500/mm^3 (1.5x109/L) during clozapine treatment. WBC counts and differential blood counts should then be performed daily and patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection.
Confirmation of the hematological values is recommended by performing two blood counts on two consecutive days; however, clozapine should be discontinued after the first blood count.
Other precautions
Eosinophilia
In the event of eosinophilia, discontinuation of clozapine is recommended if the eosinophil count rises above 3000/mm^3 (3.0x109/L); therapy should be restarted only after the eosinophil count has fallen below 1000/mm^3 (1.0x109/L).
Thrombocytopenia
In the event of thrombocytopenia, discontinuation of clozapine therapy is recommended if the platelet count falls below 50 000/mm^3 (50x109/l).
Cardiovascular disorders
Orthostatic hypotension, with or without syncope, can occur during clozapine treatment. Rarely, collapse can be profound and may be accompanied by cardiac and/or respiratory arrest. Such events are more likely to occur with concurrent use of a benzodiazepine or any other psychotropic agent and during initial titration in association with rapid dose escalation; on very rare occasions they may occur even after the first dose. Therefore, patients starting clozapine treatment require close medical supervision. Monitoring of standing and supine blood pressure is necessary during the first weeks of treatment in patients with Parkinson's disease.
Analysis of safety databases suggests that the use of clozapine is associated with an increased risk of myocarditis especially during, but not limited to, the first two months of treatment. Some cases of myocarditis have been fatal. Pericarditis/pericardial effusion and cardiomyopathy have also been reported in association with clozapine use; these reports also include fatalities.
Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first two months of treatment, and/or palpitations, arrhythmias, chest pain, and other signs and symptoms of heart failure (e.g., unexplained fatigue, dyspnoea, tachypnoea), or symptoms that mimic myocardial infarction. Other symptoms which may be present in addition to the above include flu-like symptoms. If myocarditis or cardiomyopathy is suspected, clozapine treatment should be promptly stopped and the patient immediately referred to a cardiologist.
In patients who are diagnosed with cardiomyopathy while on clozapine treatment, there is potential to develop mitral valve incompetence. Mitral valve incompetence has been reported in cases of cardiomyopathy related to clozapine treatment. These cases of mitral valve incompetence reported either mild or moderate mitral regurgitation on two-dimensional echocardiography (2DEcho). Patients with clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine.
Myocardial infarction
In addition, there have been post-marketing reports of myocardial infarction which may be fatal.
Causality assessment was difficult in the majority of these cases because of serious pre-existing cardiac disease and plausible alternative causes.
QT interval prolongation
As with other antipsychotics, caution is advised in patients with known cardiovascular disease or a family history of QT prolongation.
As with other antipsychotics, caution should be exercised when clozapine is prescribed with medicines known to increase QT (arc).
Cerebrovascular adverse events
An approximately 3-fold increased risk of cerebrovascular adverse events has been seen in randomized placebo-controlled clinical trials in the dementia population with some atypical antipsychotics. The mechanism for this increased risk is not known. An increased risk cannot be excluded for other antipsychotics or other patient populations. Clozapine should be used with caution in patients with risk factors for stroke.
Risk of thromboembolism
Since clozapine may be associated with thromboembolism, immobilization of patients should be avoided. Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs.
Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with clozapine and preventive measures undertaken.
Seizures
Patients with a history of epilepsy should be closely observed during clozapine therapy since dose-related convulsions have been reported. In such cases, the dose should be reduced and, if necessary, an anti-convulsant treatment should be initiated.
Anticholinergic effects
Clozapine exerts anticholinergic activity, which may produce undesirable effects throughout the body. Careful supervision is indicated in the presence of prostatic enlargement and narrow-angle glaucoma. Probably on account of its anticholinergic properties, clozapine has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, fecal impaction, and paralytic ileus.
On rare occasions, these cases have been fatal. Particular care is necessary for patients who are receiving concomitant medications known to cause constipation (especially those with anticholinergic properties such as some antipsychotics, antidepressants, and antiparkinsonian treatments), have a history of colonic disease or a history of lower abdominal surgery as these may exacerbate the situation. It is vital that constipation is recognized and actively treated.
Fever
During clozapine therapy, patients may experience transient temperature elevations above 38°C, with the peak incidence within the first 3 weeks of treatment. This fever is generally benign.
Occasionally, it may be associated with an increase or decrease in the WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infection or the development of agranulocytosis. In the presence of high fever, the possibility of the neuroleptic malignant syndrome (NMS) must be considered. If the diagnosis of NMS is confirmed, clozapine should be discontinued immediately and appropriate medical measures should be administered.
Metabolic changes
Atypical antipsychotic drugs, including clozapine, have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes may include hyperglycemia, dyslipidemia, and body weight gain. While atypical antipsychotic drugs may produce some metabolic changes, each drug in the class has its own specific profile.
Hyperglycaemia
Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine. A mechanism for this possible association has not yet been determined. Cases of severe hyperglycemia with ketoacidosis or hyperosmolar coma have been reported very rarely in patients with no prior history of hyperglycemia, some of which have been fatal. When follow-up data were available, discontinuation of clozapine resulted mostly in the resolution of the impaired glucose tolerance, and reinstitution of clozapine resulted in its reoccurrence. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug. The discontinuation of clozapine should be considered in patients where active medical management of their hyperglycemia has failed.
Dyslipidemia

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Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics, including clozapine. Clinical monitoring, including baseline and periodic follow-up lipid evaluations in patients using clozapine, is recommended.

Weight gain

Weight gain has been observed with atypical antipsychotic use, including clozapine.

Clinical

Monitoring of weight is recommended.

Rebound, withdrawal effects

Acute withdrawal reactions have been reported following abrupt cessation of clozapine therefore gradual withdrawal is recommended. If abrupt discontinuation is necessary (e.g., because of leucopenia), the patient should be carefully observed for the recurrence of psychotic symptoms and symptoms related to cholinergic rebounds such as profuse, sweating, headache, nausea, vomiting, and diarrhea.

Special populations

Hepatic impairment

Patients with stable pre-existing liver disorders may receive clozapine but need regular liver function tests. Liver function tests should be performed in patients in whom symptoms of possible liver dysfunction, such as nausea, vomiting, and/or anorexia, develop during clozapine therapy. If the elevation of the values is clinically relevant (more than 3 times the UNL) or if symptoms of jaundice occur, treatment with clozapine must be discontinued. It may be resumed only when the results of liver function tests are normal. In such cases, liver function should be closely monitored after the re-introduction of clozapine.

Patients aged 60 years and older

Initiation of treatment in patients aged 60 years and older is recommended at a lower dose. Orthostatic hypotension can occur with clozapine treatment and there have been reports of tachycardia, which may be sustained. Patients aged 60 years and older, particularly those with compromised cardiovascular function, may be more susceptible to these effects.

Patients aged 60 years and older may also be particularly susceptible to the anticholinergic effects of clozapine, such as urinary retention and constipation.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:

Contraindication of concomitant use

Substances known to have a substantial potential to depress bone marrow function must not be used concurrently with clozapine. Long-acting depot antipsychotics (which have myelosuppressive potential) must not be used concurrently with clozapine because these cannot be rapidly removed from the body in situations where this may be required, e.g., neutropenia.

Alcohol should not be used concomitantly with clozapine due to possible potentiation of sedation.

Precautions including dose adjustment

Clozapine may enhance the central effects of CNS depressants such as narcotics, antihistamines, and benzodiazepines. Particular caution is advised when clozapine therapy is initiated in patients who are receiving a benzodiazepine or any other psychotropic agent. These patients may have an increased risk of circulatory collapse, which, on rare occasions, can be profound and may lead to cardiac and/or respiratory arrest. It is not clear whether cardiac or respiratory collapse can be prevented by dose adjustment.

Because of the possibility of additive effects, caution is essential in the concomitant administration of drugs possessing anticholinergic, hypotensive, or respiratory depressant effects.

Owing to its anti-alpha-adrenergic properties, clozapine may reduce the blood-pressure-increasing effect of norepinephrine or other predominantly alpha-adrenergic agents and reverse the pressor effect of epinephrine.

Concomitant administration of substances known to inhibit the activity of some cytochrome P450 isozymes may increase the levels of clozapine, and the dose of clozapine may need to be reduced to prevent undesirable effects. This is more important for CYP 1A2 inhibitors such as caffeine perazine and the selective serotonin reuptake inhibitor fluvoxamine. Some of the other serotonin reuptake inhibitors such as fluoxetine, paroxetine, and, to a lesser degree, sertraline CYP 2D6 inhibitors, and, as a consequence, major pharmacokinetic interactions with clozapine are less likely. Similarly, pharmacokinetic interactions with CYP 3A4 inhibitors such as azole antimycotics, cimetidine, erythromycin, and protease inhibitors are unlikely, although some have been reported. Hormonal contraceptives (including combinations of estrogen and progesterone or progesterone only) are CYP 1A2, CYP 3A4, and CYP 2C19 inhibitors. Therefore, initiation or discontinuation of hormonal contraceptives may require dose adjustment of clozapine according to the individual medical need. Because the plasma concentration of clozapine is increased by caffeine intake and decreased by nearly 50% following a 5-day caffeine-free period, dosage changes of clozapine may be necessary when there is a change in caffeine-drinking habit. In cases of sudden cessation of smoking, the plasma clozapine concentration may be increased, thus leading to an increase in adverse effects.

Cases have been reported of an interaction between citalopram and clozapine, which may increase the risk of adverse events associated with clozapine. The nature of this interaction has not been fully elucidated.

Concomitant administration of substances known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine, leading to reduced efficacy. Substances known to induce the activity of cytochrome P450 enzymes and with reported interactions with clozapine include, for instance, carbamazepine (not to be used concomitantly with clozapine, due to its myelosuppressive potential), phenytoin, and rifampicin. Known inducers of CYP1A2 such as omeprazole may lead to decreased clozapine levels. The potential for reduced efficacy of clozapine should be considered when it is used in combination with these substances.

Other

Concomitant use of lithium or other CNS-active agents may increase the risk of the development of neuroleptic malignant syndrome (NMS).

Rare but serious reports of seizures, including the onset of seizures in non-epileptic patients, and isolated cases of delirium where clozapine was co-administered with valproic acid have been reported. These effects are possibly due to a pharmacodynamic interaction, the mechanism of which has not been determined.

Caution is called for in patients receiving concomitant treatment with other substances which are either inhibitors or inducers of the cytochrome P450 isozymes. With tricyclic antidepressants, phenothiazines, and type 1C antiarrhythmics, which are known to bind to cytochrome P450 2D6, no clinically relevant interactions have been observed thus far.

As with other antipsychotics, caution should be exercised when clozapine is prescribed with medicines known to increase QTc interval (QTC) or cause electrolyte imbalance.

Reference to the most common drug interactions with Clozapine

DRUG	INTERACTIONS	COMMENTS
Bone marrow suppressants (e.g., carbamazepine, chloramphenicol, sulphonamides (e.g., FR-trimoxazole), pyrazolone analgesics (e.g. phenylbutazone), penicillamine, cytotoxic agents and long-acting depot injections of antipsychotics	Interact to increase the risk and/or severity of bone marrow suppression.	Clozapine **must not be used** concomitantly with other agents having a well-known potential to suppress bone marrow function.
Benzodiazepines	Concomitant use may increase the risk of circulatory collapse, which may lead to cardiac and/or respiratory arrest.	Whilst the occurrence is rare, caution is advised when using these drugs together. Reports suggest that respiratory depression and collapse are more likely to occur at the start of this combination or when clozapine is added to an established benzodiazepine regimen.
Anticholinergics	Clozapine potentiates the action of these drugs through additive anticholinergic activity.	Observe patients for anticholinergic side effects, e.g., constipation, especially when used to help control hypersalivation.
Antihypertensives	Clozapine can potentiate the hypotensive effects of these drugs due to their sympathomimetic and antagonistic effects.	Caution is advised if clozapine is used concomitantly with antihypertensive agents. Patients should be advised of the risk of hypotension, especially during the period of initial dose titration.
Alcohol, MAOIs, CNS depressants, including narcotics and benzodiazepines	Enhanced central effects. Additive CNS depression and cognitive and motor performance interference when used in combination with these substances.	Caution is advised if clozapine is used concomitantly with other CNS active agents. Advise patients of the possible additive sedative effects and caution them not to drive or operate machinery.
Highly protein-bound drugs (e.g., warfarin and digoxin)	Clozapine may cause an increase in the plasma concentration of these substances due to displacement from plasma proteins.	Patients should be monitored for the occurrence of side effects associated with these substances, and doses of the protein-bound substance adjusted, if necessary
Phenytoin	Addition of phenytoin to clozapine regimen may cause a decrease in the clozapine plasma concentrations.	If phenytoin must be used, the patient should be monitored closely for a worsening or recurrence of psychotic symptoms.
Lithium	Concomitant use can increase the risk of the development of neuroleptic malignant syndrome (NMS).	Observe for signs and symptoms of NMS
CYP1A2-inducing substances (e.g., omeprazole)	Concomitant use may decrease clozapine levels.	Potential for reduced efficacy of clozapine should be considered
CYP1A2 inhibiting substances e.g., fluvoxamine, caffeine, ciprofloxacin, perazine, or hormonal contraceptives (CYP1A2, CYP3A4, CYP2C19)	Concomitant use may increase clozapine levels.	Potential for increase in adverse effects. Care is also required upon cessation of concomitant CYP1A2 or CYP3A4 inhibiting medications as there may be a decrease in clozapine levels. The effect of CYP2C19 inhibition may be minimal.

Pregnancy

For clozapine, there are only limited clinical data on exposed pregnancies. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition, or postnatal development. Caution should be exercised when prescribing to pregnant women.

Neonates exposed to antipsychotics (including clozapine) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Breastfeeding

Animal studies suggest that clozapine is excreted in breast milk and has an effect on the nursing infant; therefore, mothers receiving Clozapine (Clozadin) should should not breastfeed.

Fertility

Limited data available on the effects of clozapine on human fertility are inconclusive. In male and female rats, clozapine did not affect fertility when administered up to 40 mg/kg, corresponding to a human equivalence dose of 6.4 mg/kg or approximately a third of the maximum permissible adult human dose.

Women of childbearing potential

A return to normal menstruation may occur as a result of switching from other antipsychotics to clozapine. Adequate contraceptive measures must therefore be ensured in women of childbearing potential.

Effects on the ability to drive and use machines

Owing to the ability of Clozapine (Clozadin) to cause sedation and lower the seizure threshold, activities such as driving or operating machinery should be avoided, especially during the initial weeks of treatment.

ADVERSE DRUG REACTIONS:

Summary of the safety profile

For the most part, the adverse event profile of clozapine is predictable from its pharmacological properties. An important exception is its propensity to cause agranulocytosis.

Because of this risk, its use is restricted to treatment-resistant schizophrenia and psychosis occurring during the course of Parkinson's disease in cases where standard treatment has failed.

While blood monitoring is an essential part of the care of patients receiving clozapine, the physician should be aware of other rare but serious adverse reactions, which may be diagnosed in the early stages only by careful observation and questioning of the patient in order to prevent morbidity and mortality.

The most serious adverse reactions experienced with clozapine are agranulocytosis, seizure, cardiovascular effects, and fever. The most common side effects are drowsiness/sedation, dizziness, tachycardia, constipation, and hypersalivation.

Data from the clinical trial experience showed that a varying proportion of clozapine-treated patients (from 7.1 to 15.6%) were discontinued due to an adverse event, including only those that could be reasonably attributed to clozapine. The more common events considered to be causes of discontinuation were leukopenia, somnolence, dizziness (excluding vertigo), and psychotic disorder.

Blood and lymphatic system

Development of granulocytopenia and agranulocytosis is a risk inherent to clozapine treatment.

Although generally reversible on withdrawal of treatment, agranulocytosis may result in sepsis and can prove fatal. Because immediate withdrawal of treatment is required to prevent the development of life-threatening agranulocytosis, monitoring of the WBC count is mandatory.

Metabolic and nutritional disorders

Impaired glucose tolerance and/or development or exacerbation of diabetes mellitus has been reported rarely during treatment with clozapine. On very rare occasions, severe hyperglycemia, sometimes leading to ketoacidosis / hyperosmolar coma, has been reported in patients on clozapine treatment with no prior history of hyperglycemia. Glucose levels normalized in most patients after discontinuation of clozapine and in a few cases, hyperglycemia recurred when treatment was reinitiated. Although most patients had risk factors for non-insulin-dependent diabetes mellitus, hyperglycemia has also been documented in patients with no known risk factors.

Nervous system disorders

The very common adverse reactions observed include drowsiness/sedation, and dizziness.

Clozapine can cause EEG changes, including the occurrence of spike and wave complexes. It lowers the seizure threshold in a dose-dependent manner and may induce myoclonic jerks or generalized seizures. These symptoms are more likely to occur with rapid dose increases and in patients with pre-existing epilepsy. In such cases the dose should be reduced and, if necessary, anticonvulsant treatment initiated. Carbamazepine should be avoided because of its potential to depress bone marrow function, and with other anticonvulsants, the possibility of a pharmacokinetic interaction should be considered.

In rare cases, patients treated with clozapine may experience delirium.

Very rarely, tardive dyskinesia has been reported in patients on clozapine who had been treated with other antipsychotic agents. Patients in whom tardive dyskinesia developed with other antipsychotics have improved on clozapine.

Cardiac disorders

Tachycardia and postural hypotension with or without syncope may occur, especially in the initial weeks of treatment. The prevalence and severity of hypotension are influenced by the rate and magnitude of dose titration. Circulatory collapse as a result of profound hypotension, in particular, related to aggressive titration, with the possible serious consequences of cardiac or pulmonary arrest, has been reported with clozapine.

A minority of clozapine-treated patients experience ECG changes similar to those seen with other antipsychotics, including S-T segment depression and flattening or inversion of T waves, which normalize after discontinuation of clozapine. The clinical significance of these changes is unclear.

However, such abnormalities have been observed in patients with myocarditis, which should therefore be considered.

Isolated cases of cardiac arrhythmias, pericarditis/pericardial effusion, and myocarditis have been reported, some of which have been fatal. The majority of the cases of myocarditis occurred within the first 2 months of initiation of therapy with clozapine. Cardiomyopathy generally occurred later in the treatment.

Eosinophilia has been co-reported with some cases of myocarditis (approximately 14%) and pericarditis / pericardial effusion; it is not known, however, whether eosinophilia is a reliable predictor of carditis.

Signs and symptoms of myocarditis or cardiomyopathy include persistent tachycardia at rest, palpitations, arrhythmias, chest pain, and other signs and symptoms of heart failure (e.g., unexplained fatigue, dyspnoea, tachypnoea), or symptoms that mimic myocardial infarction. Other symptoms which may be present in addition to the above include flu-like symptoms.

Sudden, unexplained deaths are known to occur among psychiatric patients who receive conventional antipsychotic medication but also among untreated psychiatric patients. Such deaths have been reported very rarely in patients receiving clozapine.

Vascular disorders

Rare cases of thromboembolism have been reported.

Respiratory system

Respiratory depression or arrest has occurred very rarely, with or without circulatory collapse.

Gastrointestinal system

Constipation and hypersalivation have been observed very frequently, and nausea and vomiting frequently. Very rarely ileus may occur. Rarely clozapine treatment may be associated with dysphagia. Aspiration of ingested food may occur in patients presenting with dysphagia or as a consequence of acute overdosage.

Hepatobiliary disorders

Transient, asymptomatic elevations of liver enzymes and rarely, hepatitis and cholestatic jaundice may occur. Very rarely, fulminant hepatic necrosis has been reported. If jaundice develops, clozapine should be discontinued. In rare cases, acute pancreatitis has been reported.

Renal disorders

Isolated cases of acute interstitial nephritis have been reported in association with clozapine therapy.

Reproductive and breast disorders

Very rare reports of priapism have been received.

General disorders

Cases of the neuroleptic malignant syndrome (NMS) have been reported in patients receiving clozapine either alone or in combination with lithium or other CNS-active agents.

Acute withdrawal reactions have been reported.

OVERDOSE AND TREATMENT:

In cases of acute intentional or accidental clozapine overdose for which information on the outcome is available, mortality to date is about 12%. Most of the fatalities were associated with cardiac failure or pneumonia caused by aspiration and occurred at doses above 2000 mg. There have been reports of patients recovering from an overdose in excess of 10 000 mg. However, in a few adult individuals, primarily those not previously exposed to clozapine, the ingestion of doses as low as 400 mg led to life-threatening comatose conditions and, in one case, to death. In young children, the intake of 50 to 200 mg resulted in strong sedation or coma without being lethal.

Signs and symptoms

Drowsiness, lethargy, areflexia, coma, confusion, hallucinations, agitation, delirium, extrapyramidal symptoms, hyperreflexia, convulsions; hypersalivation, mydriasis, blurred vision, thermolability; hypotension, collapse, tachycardia, cardiac arrhythmias; aspiration pneumonia, dyspnoea, respiratory depression or failure.

Treatment

There are no specific antidotes for clozapine.

Gastric lavage and/or administration of activated charcoal within the first 6 hours after the ingestion of the drug. Peritoneal dialysis and hemodialysis are unlikely to be effective. Symptomatic

treatment under continuous cardiac monitoring, surveillance of respiration, monitoring of electrolytes, and acid-base balance. The use of epinephrine should be avoided in the treatment of hypotension because of the possibility of a 'reverse epinephrine' effect.

Close medical supervision is necessary for at least 5 days because of the possibility of delayed reactions.

CAUTION:

Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

"For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph.
Seek medical attention immediately at the first sign of any adverse drug reaction."

STORAGE CONDITION:

Store at temperatures not exceeding 30°C.

KEEP ALL MEDICINES OUT OF REACH OF CHILDREN.

AVAILABILITY:

Alu/Clear PVC Blister Pack x 10's (Box of 50's)

Clozapine (Clozadin) 25 mg:
DRP-11092-01
Date of First Authorization: October 27, 2022
Date of Revision of Package Insert: March 15, 2023

Clozapine (Clozadin) 100 mg:
DRP-11091-01
Date of First Authorization: October 26, 2022
Date of Revision of Package Insert: March 15, 2023

Manufactured by:
REMEDICA LTD.
Aharnon Street, Limassol Industrial Estate, Building 1-Main, Building 2-Penicillins, Building 4-Cephalosporins, Building 5-Anti-Cancer/Hormones, Building 10-Anti-Cancer, Limassol, 3056, Cyprus

Imported by:
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Clozapine
05 / 04 / 2023

N.S.
Final Size: 310 x 400mm
Color: Black

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